

Atazanavir

Brand Name: Reyataz

Drug Class: Protease Inhibitors



Drug Description

Atazanavir, formerly known as BMS-232632, is an azapeptide protease inhibitor (PI) of HIV-1 protease. [1]

HIV/AIDS-Related Uses

Atazanavir sulfate was approved by the FDA on June 20, 2003, for the treatment of HIV-1 infection in combination with other antiretroviral agents.[2]

The FDA based its approval of atazanavir on data from two Phase 2 48-week trials and from 24 to 48 week data from Phase 3 studies. Results from these trials showed a decrease in viral load and an increase in CD4 cell counts in patients taking atazanavir in combination with other antiretroviral agents.[3]

The use of atazanavir sulfate may be considered in antiretroviral-experienced adults with HIV strains that are expected to be susceptible to atazanavir sulfate by genotypic and phenotypic testing.[4]

Pharmacology

Atazanavir is an azapeptide PI that selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, preventing formation of mature virions. Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC₅₀) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. Two-drug combination studies with atazanavir showed additive to antagonistic antiviral activity in vitro with abacavir and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, and nevirapine and additive antiviral activity in vitro with the PIs amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, the nucleoside reverse transcriptase inhibitors didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine, the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and

ribavirin, without enhanced cytotoxicity.[5]

Atazanavir is rapidly absorbed, with a median time to maximum plasma concentration of approximately 2.5 hours in healthy people and 2 hours in HIV infected individuals. Administration with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single dose of 400 mg atazanavir with a light meal resulted in a 70% increase in the area under the plasma concentration-time curve (AUC) and a 57% increase in mean maximum plasma concentration (C_{max}) relative to the fasting state, while administration with a high-fat meal resulted in a mean increase in AUC of 35% and no change in C_{max} relative to the fasting state. Administration with either a light or high fat meal decrease the coefficient of variation of AUC and C_{max} by approximately one-half, compared to the fasting state.[6] Atazanavir demonstrates nonlinear pharmacokinetics, with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200 to 800 mg once daily. Steady-state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold. The pharmacokinetics of atazanavir in pediatric patients are under investigation.[7]

In a multiple-dose study in HIV infected patients taking 400 mg atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid (CSF) and semen. The CSF/plasma ratio for atazanavir ranged between 0.0021 and 0.0226; the seminal fluid/plasma ratio ranged between 0.11 and 4.42.[8]

Atazanavir is in FDA Pregnancy Category B. There have been no adequate and well-controlled studies of atazanavir in pregnant women. Atazanavir should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. No significant effects on mating, fertility, or early embryonic development were observed in rats given daily doses up to two times the human clinical dose of 400 mg atazanavir once daily. In studies with rabbits and rats given doses producing drug exposure levels up to two times the human clinical dose, atazanavir did not produce teratogenic effects. However, in pre- and postnatal

Pharmacology (cont.)

studies of rats given atazanavir at maternally toxic exposure levels, two times the human clinical dose caused weight loss or weight gain suppression in the offspring. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents. Physicians may register their patients by calling 1-800-258-4263 or online at <http://www.APREgistry.com>. [9]

It is not known whether atazanavir is secreted in human breast milk; however, it is distributed into the milk of rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in the nursing infant, mothers should be instructed not to breastfeed if they are receiving atazanavir. [10]

Atazanavir is 86% bound to human serum proteins; protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). [11] Atazanavir is extensively metabolized in the liver by CYP3A and inhibits CYP3A and UGT1A1. The major biotransformation pathways of atazanavir consist of mono-oxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir and its metabolites include glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites in plasma have been characterized, neither of which demonstrated in vitro antiviral activity. Elimination half-life of healthy or HIV infected adults is approximately 7 hours following a 400 mg daily dose of atazanavir with a light meal. Atazanavir is primarily eliminated in the feces (79%) and the urine (13%). Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. [12]

Atazanavir is highly selective for HIV-1 protease and exhibits cytotoxicity at concentrations 6,500- to 23,000-fold higher than concentrations required for therapeutic antiviral activity. [13] Treatment-naïve patients developed a characteristic I50L mutation but retained in vitro susceptibility to other PIs. In contrast, treatment-experienced patients who experienced virologic failure developed mutations

that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease mutations to develop included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Generally, if multiple PI resistance mutations were present in the HIV-1 of the patient at baseline, atazanavir resistance developed through mutations associated with resistance to other PIs and could include the development of the I50L mutation. [14]

Adverse Events/Toxicity

Adverse effects observed with clinical use of atazanavir include allergic reaction; new onset or exacerbation of existing diabetes mellitus or hyperglycemia; asymptomatic hyperbilirubinemia, including yellow eyes or skin; lactic acidosis; PR interval prolongation; abdominal pain; back pain; increased cough; depression; diarrhea; headache; jaundice; lipodystrophy and fat redistribution; nausea; scleral icterus; or vomiting. Incidences of these adverse effects cannot be determined because of insufficient data. [15]

Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to the inhibition of UDP-flucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. [16]

Rash occurred in 21% of patients taking atazanavir in controlled clinical trials. The median time to onset of rash was 8 weeks after initiation of atazanavir therapy, and the median duration of rash was 1.3 weeks. Rashes were generally mild to moderate maculopapular skin eruptions. Dosing with atazanavir was often continued without interruption in patients who developed rash. Atazanavir should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome and erythema multiforme have been reported in patients receiving atazanavir. [17]

Atazanavir is principally metabolized by the liver; caution should be exercised when administering this drug to patients with hepatic impairment

Adverse Events/Toxicity (cont.)

because atazanavir concentrations may be increased. Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation.[18]

Increased bleeding, including spontaneous skin hematomas and hemarthrosis, have been observed in patients with hemophilia type A and B treated with PIs. In some patients additional factor VIII was required. In many of the reported cases, treatment with PIs was continued or restarted. A causal relationship between PI therapy and these episodes has not been established.[19]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[20]

Immune reconstitution syndrome has been reported in some patients treated with combination antiretroviral therapy, including atazanavir. During the initial phase of combination antiretroviral therapy, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.[21]

Drug and Food Interactions

Atazanavir should be administered with food.[22]

Atazanavir should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A, UGT1A1, or CYP2C8. Coadministration of atazanavir and drug primarily metabolized by CYP3A (e.g., calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors), CYP2C8, or UGT1A1 (e.g., irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse events. Coadministration of atazanavir and drugs that inhibit CYP3A may

increase atazanavir plasma concentrations.[23]

Indinavir should not be coadministered concomitantly, as indirect hyperbilirubinemia may result if the drugs are taken together. Coadministration of atazanavir with efavirenz decreases atazanavir exposure. It is recommended that atazanavir be administered with ritonavir when atazanavir is to be coadministered with efavirenz as part of an HIV treatment regimen.[24] In an attempt to overcome the effects of CYP3A4 induction when coadministered with efavirenz, atazanavir has been paired with various doses of ritonavir. When ritonavir (100 mg once daily) was added to a 300 mg once daily dose of atazanavir, atazanavir C_{min} was increased approximately 10-fold above that observed in the absence of ritonavir, while the AUC and C_{max} were increased 3.3- and 1.8-fold, respectively. This ritonavir-augmented exposure appears likely to permit atazanavir and efavirenz coadministration.[25] Another NNRTI, nevirapine, should not be administered with atazanavir because nevirapine is an inducer of CYP3A and is expected to decrease atazanavir concentrations.[26]

Ritonavir increases atazanavir concentrations when the two drugs are taken concurrently; reduced dosing of atazanavir should be considered. Concurrent administration of atazanavir and saquinavir increases saquinavir concentrations; dosing for coadministration with respect to efficacy and safety have not been established.[27]

A pharmacokinetic study of nucleoside analogue interactions in healthy individuals showed that coadministration of atazanavir and didanosine reduces atazanavir exposure by fourfold as assessed by AUC.[28] Coadministration of atazanavir with didanosine buffered tablets results in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given with food 2 hours before or 1 hour after didanosine buffered formulations. Simultaneous administration of enteric-coated didanosine and atazanavir with food results in a didanosine exposure; therefore, atazanavir and enteric-coated didanosine should be administered at different times.[29]

Tenofovir may decrease the AUC and C_{min} of atazanavir if the two medications are taken

Drug and Food Interactions (cont.)

concurrently. When coadministered with tenofovir, it is recommended that 300 mg atazanavir be given with 100 mg ritonavir and 300 mg tenofovir, all as a single dose with food. Atazanavir should not be coadministered with tenofovir unless it is administered along with ritonavir.[30]

Concurrent administration of atazanavir with amiodarone, lidocaine, or quinidine may increase antiarrhythmic drug concentrations, resulting in potentially serious or life-threatening adverse events. Caution and concentration monitoring is suggested.[31]

Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H₂-receptor antagonists are administered concurrently with atazanavir. Concomitant administration of H₂-receptor antagonists and atazanavir may lead to loss of therapeutic effect and the development of resistance.[32] In a drug interaction study of atazanavir 300 mg and ritonavir 100 mg coadministered with the proton-pump inhibitor omeprazole 40 mg, a 76% reduction in atazanavir AUC and a 78% reduction in atazanavir C_{min} were observed. Coadministration of these agents is not recommended by the manufacturer. Because no data are available on the omeprazole 20 mg formulation, the manufacturer advises against its coadministration as well. Reduced plasma concentrations are expected if H₂-antagonists are coadministered with atazanavir, so these drugs should be given as far apart as possible, preferably 12 hours apart.[33]

Concurrent use of atorvastatin and atazanavir may increase atorvastatin concentrations, resulting in an increased risk for myopathy, including rhabdomyolysis; this combination should be used with caution. Lovastatin or simvastatin should not be administered concomitantly with atazanavir because such serious reactions such as myopathy may occur with concomitant use.[34]

Increased concentrations of clarithromycin may cause QTc prolongations if atazanavir is taken concurrently with clarithromycin. When atazanavir is concurrently administered with clarithromycin,

concentrations of the active metabolite 14-OH clarithromycin are significantly reduced while concentrations of atazanavir are increased. Dose reduction of clarithromycin should be considered. Alternative therapy for indications other than *Mycobacterium avium* infections should be considered.[35]

Concurrent use of atazanavir with cyclosporine, sirolimus, or tacrolimus may increase immunosuppressant drug concentration. Monitoring for therapeutic concentrations of these drugs is recommended when any of these are administered concomitantly with atazanavir.[36]

Coadministration of atazanavir and diltiazem resulted in a twofold increase in diltiazem AUC; a dosage reduction of diltiazem is recommended, along with electrocardiogram (ECG) monitoring. Concurrent use of atazanavir with calcium channel blockers (such as felodipine, nifedipine, or verapamil) may increase calcium channel blocker drug concentration. Dose titration of the calcium channel blocker is recommended, along with ECG monitoring.[37]

Coadministration of atazanavir with oral contraceptives containing ethinyl estradiol and norethindrone may increase the concentration of the oral contraceptives. Decreased high density lipoprotein (HDL) or increased insulin resistance may be associated with increased concentration of norethindrone, particularly in diabetic women. The lowest effective dose of oral contraceptive should be given to patients who require both atazanavir and an oral contraceptive.[38]

Coadministration of atazanavir and rifabutin resulted in an increase of rifabutin concentrations. A dosage reduction of rifabutin is recommended.[39] Caution should be used when atazanavir and rifampin are taken concurrently. Rifampin decreases plasma concentrations and AUC of most PIs by approximately 90%. This may result in loss of therapeutic effect of atazanavir and the development of viral resistance.[40]

Caution should be used when prescribing PDE5 inhibitors for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) to patients receiving PIs, including atazanavir. Coadministration of a PI with

Drug and Food Interactions (cont.)

a PDE5 inhibitor is expected to substantially increase the adverse events associated with PDE5 inhibitors, including hypotension, visual changes, and priapism. Dosage reduction may be necessary and patients should be monitored for adverse events.[41]

Concurrent administration of atazanavir and tricyclic antidepressants may increase antidepressant concentrations, resulting in the potential for serious or life-threatening adverse events. Concentration monitoring of the antidepressant is recommended. Concurrent administration of atazanavir and warfarin may increase warfarin concentrations, which may result in the potential for serious or life-threatening bleeding events.[42]

There were no clinically significant effects on the AUC of zidovudine, lamivudine, or stavudine when administered concomitantly with atazanavir, and no dosage adjustment was necessary.[43]

In healthy people, a drug interaction study has shown that ritonavir significantly increases levels plasma of fluticasone propionate, resulting in significantly decreased serum cortisol concentrations if these two drugs are taken concurrently. Concomitant use of atazanavir with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasal fluticasone propionate. Coadministration of atazanavir with ritonavir and fluticasone propionate is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. Alternatives to fluticasone should be considered, particularly in cases of long-term use.[44]

Coadministration of the antidepressant trazodone and ritonavir has resulted in nausea, dizziness, hypotension, and syncope. Concomitant use of atazanavir with ritonavir and trazodone is expected to produce the same effects. Concomitant use of the antidepressant trazodone and atazanavir with or without ritonavir may increase plasma

concentrations of trazodone. Such a combination should be used with caution and a lower dose of trazodone should be considered.[45]

Coadministration of atazanavir is contraindicated with rifampin, irinotecan, bepridil, lovastatin, simvastatin, indinavir, proton-pump inhibitors including omeprazole and St. John's wort.[46]

Contraindications

Atazanavir is contraindicated in patients with known hypersensitivity to atazanavir or any of its ingredients. Coadministration of atazanavir is contraindicated with drugs that are highly dependent on CYP3A for clearance, including benzodiazepines (midazolam, triazolam); ergot derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine); gastrointestinal (GI) motility agents (cisapride); and neuroleptics (pimozide).[47]

Because atazanavir has been shown to prolong the PR interval of the electrocardiogram, risk-benefit should be considered in patients with pre-existing atrioventricular (AV) conduction abnormalities. Risk-benefit should also be considered in patients with obesity, diabetes mellitus, or hyperglycemia; hepatic function impairment, elevated transaminase levels, or hepatitis B or C infection; or type A or B hemophilia.[48]

Clinical Trials

For information on clinical trials that involve Atazanavir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Atazanavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[49]

Dosage Form: Capsules containing atazanavir 100, 150, or 200 mg.[50]

For antiretroviral-naïve patients, the recommended dose of atazanavir is 400 mg (two 200 mg capsules) once daily. The recommended dose of atazanavir in antiretroviral-experienced patients is 300 mg (two

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Dosing Information (cont.)

150 mg capsules) taken with ritonavir 100 mg once daily with food. When coadministered with efavirenz, it is recommended that atazanavir 300 mg and ritonavir 100 mg be given with efavirenz 600 mg (all as a single daily dose). When coadministered with tenofovir, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir 300 mg, all in a single daily dose with food. Dosing modification may be appropriate for coadministration of atazanavir and other antiretroviral agents; recommendations for dosing modification are included in the Reyataz prescribing information.[51]

A dose reduction to 300 mg once daily should be considered for patients with moderate hepatic insufficiency (Child-Pugh Class B).[52]

Storage: Store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[53]

Chemistry

CAS Name: 2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-((4-(2-pyridinyl)phenyl)methyl)-, dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1) (salt) (atazanavir sulfate)[54]

CAS Number: 229975-97-7 (atazanavir sulfate)[55]

Molecular formula: C₃₈H₅₂N₆O₇·H₂O₄·S (atazanavir sulfate)[56]

C56.8%, H6.8%, N10.5%, O21.9%, S4.0% (atazanavir sulfate)[57]

Molecular weight: 802.93 (atazanavir sulfate)[58]

Physical Description: White to pale yellow crystalline powder.[59]

Solubility: Slightly soluble in water (4 to 5 mg/ml, free base equivalent), with the pH of a saturated solution in water of about 1.9 at 24 +/- 3 C.[60]

Other Names

BMS-232632-05 (atazanavir sulfate)[61]

BMS 232632 (atazanavir)[62]

ATZ[63]

ATV[64]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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